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TITLE: Phase I/II Pilot Study to Assess Toxicity and Efficacy of Chinese Herbs to Treat Hot Flashes and Menopausal Symptoms for Women with a History of Breast Cancer

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13. Abstract ***(Maximum 200 Words)*** *(abstract should contain no proprietary or confidential information)*

The goal of the study is to assess the safety and feasibility of a Chinese herbal formula, MF101, in alleviating hot flashes and other symptoms associated with menopause. Our group has experienced a delay in initiating the funded trial due to concerns raised by the Food and Drug Administration (FDA). In the original grant submitted to the Department of Defense (DOD), the population of women to be studied were women with a history of breast cancer. Because an Investigational New Drug License (IND) was obtained from the FDA for MF101, the herbal formula to be given to women participating in the study, the same grant application was submitted to the FDA. The primary concern addressed by the FDA was the potential estrogenic effects of MF101, specifically the relationship of estrogen and increased risk of breast cancer recurrence. The FDA placed a clinical hold on MF101, thereby delaying the study. Additionally, the FDA stated that safety data on hormonal drugs are obtained over a 30-day period and this time frame is enough to observe any physiologic or biological estrogenic changes. In short, it was agreed that the study would be conducted with healthy women over a 30-day period. Amendments to the protocol have been approved by the FDA. The Surgeon General's Human Subjects Research Review Board recently approved the above-mentioned changes, and suggested further edits to the protocol and consent form. These latter edits will be submitted to the DOD this week and, following final approval, will be submitted to the UCSF Institutional Review Board. We hope to begin the study as soon as possible.

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Summary

We have experienced a delay in beginning the funded trial due to concerns addressed by the FDA and DOD. The following is a brief summary of our communications over the past several months, and a copy of the exchanges (including letters and email) are included as Appendix A.

The original grant application to the DOD involved conducting a phase I/II trial of MF101 in order to obtain safety and early toxicity studies in women with a history of breast cancer who are experiencing symptoms such as hot flashes, night sweats, and mood swings. There are currently no satisfactory treatments for women with a history of breast cancer who are experience symptoms associated with menopause.

During the grant application process with the DOD, our group applied for a an Investigational New Drug License (IND) from the Food and Drug Administration (FDA) for the formulation to be used in the trial, MF101. Our application to the FDA was based on the same trial proposed to the DOD. Our previous experience with the FDA was very straightforward and uncomplicated, and we were able to provide data on prior herbal use in humans to demonstrate early safety in order to conduct trials in humans.

Unfortunately, the FDA felt that, though herbs have been used in traditional Chinese medicine (TCM) for centuries, the specific formulation of MF101 was based on the practice of Isaac Cohen, L.Ac., and was not sufficient data for demonstration of safety. The greatest concern of the FDA was a probable phytoestrogenic effect of MF101 in women with a history of breast cancer and, further, the potential increase in cancer recurrence due to estrogen. A clinical hold was placed on MF101 until further proof of efficacy was obtained, either through animal studies or patient testimonials.

We provided the FDA with affidavits signed by 50 patients who have been using MF101. The FDA still felt uncomfortable with granting us the full IND for the suggested phase I/II protocol, and requested that we conduct an early safety trial on 20 healthy women for 30 days. Our team argued that a duration of 30 days was too short to observe the true safety of MF101 relative to its possible estrogenic effect. The FDA countered that all hormonal drugs are initially tested for safety for a period of 30 days, and that 30 days seems to be sufficient to detect major estrogenic changes. Since the estrogenic effect that truly concerns us in women with breast cancer deals with the long term increase in risk of breast cancer recurrence, thrombogenic disorders, and uterine cancer risk that could be detected only in a phase III trial, we felt that conducting a short safety trial in women would suffice in order to guarantee the commencement of the trial we originally proposed.

Currently, the protocol amendments requested by the FDA have been approved. The DOD has approved the revised 30-day study in healthy women, but has requested changes to the protocol and consent form. Those edits are being submitted to the DOD this week.

Following approval of the revised protocol and consent form by the DOD and the UCSF Institutional Review Board, we are planning to open the trial on 20 healthy women as soon as possible.